Parkinson's Disease and COVID-19: Treatment and Patient Management During a Pandemic

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Ethics Statement

The study does not involve any kind of animal trial and human trial.

Abstract

One of the most remarkable health problems we have faced since the World War II is the COVID-19 outbreak. This review article discusses insights from basic science as well as clinical perspectives on COVID-19 disease with a specific concern on Parkinson's disease (PD). Patients with COVID-19 have compromised immunity, especially in an aged population suffering from PD. The 1st report on the relationship between COVID-19 and PD comes from the research on antibodies against four antigens of COVID-19 in Cerebrospinal Fluid (CSF) of normal controls compared to patients with neurological illnesses, especially PD. Unfortunately, identification of COVID-19 is difficult in PD patients because PD is often preceded by anosmia, which is a common feature of COVID-19. Presently, no disease-modifying treatment is available for PD. But for temporary relief, the treatment is composed of dopaminergic drugs like levodopa and PD patients with COVID-19 are treated with favipiravir, amantadine etc. where amantadine was the first FDA-approved medicine in the United States that indicates dual function in the treatment of both diseases. This review also discusses the COVID-19 negative impact on PD patients due to lockdown/isolation. To conclude, this review is mainly focused on the COVID-19 and PD relationship, consequences of PD patients infected with COVID-19, treatment options and COVID-19 impact on PD patients.

Keywords: COVID-19, Parkinson's disease, antibodies, anosmia, amantadine, lockdown.

Dedication

This work is dedicated to my parents for their love and support.

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List of Acronyms

WHO	World Health Organization
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
KP	Kynurenine Pathway
FPV	Favipiravir
CQ	Chloroquine
HCQ	Hydroxychloroquine
AZM	Azithromycin
DBS	Deep Brain Stimulation
LCIG	Levodopa-Carbidopa Intestinal Gel
UPDRS	Unified Parkinson's Disease Rating Scale
CTSL	Cathepsin L

Glossary

UPDRS:	It is the most widely applied rating instrument for Parkinson disease. It is used to follow the longitudinal course of Parkinson's disease.
Senescent cells:	Senescent cells are cells that can no longer divide or support the tissue they are part of. This is a permanent state of cell cycle arrest brought on by cellular stress. A senescent cell is in its twilight: not quite dead, but not functioning as it once did.

Chapter 1

Introduction

1.1 Background

In this era, the remarkable problem people have faced since the Second World War is the COVID-19 outbreak that has become a widespread health crisis. In 2019, this new coronavirus eruption called COVID-19 was identified in China and later around the world. As of 11:04 a.m. CET (Central European Time) on September 20, 2021, there have been two hundred twenty-nine million two hundred ninety-seven thousand eighty-five (229,297,085) confirmed cases of COVID-19 reported to WHO by national authorities, including four million seven hundred five thousand five hundred eighty-six (4,705,586) deaths. The disease has spread to all continents, and cases are increasing day by day that is causing social, economic, and political problems and leaving a deep scar (Amin Tabish, 2020).

It is the most infectious respiratory disease originated from the Severe Acute Respiratory Syndrome-Coronavirus-2. It is spread from one human to another through droplets when a COVID-19 infected person coughs, sneezes, or speaks (*WHO*, 2020) and is a member of the Coronaviridae family that contains a group of enveloped, positive-sensed, single-stranded RNA viruses (Ye et al., 2020). At first, the spike (S) protein of the virus attaches to the cell. After that, it binds to various host proteins that help its entrance (Sulzer et al., 2020).

There are some specific considerations for elderly people because of the raised susceptibility of patients with a chronic disease that additionally includes brain disorders such as PD (Helmich & Bloem, 2020). It is a chronic neurological condition marked by a wide range of motor as well as a non-motor symptoms (Jankovic, 2008) and characterized by the onset of

asymmetric rigidity along with bradykinesia, with or without rest tremor (Keener & Bordelon, 2016).

However, PD symptoms like balance/fall problems, difficulty swallowing, urinary tract dysfunction, and weight loss can cause general weakness and raise the chance of complications from COVID-19 infection. In addition, throughout the COVID-19 lockdowns, motor and non-motor symptoms were exaggerated in PD patients who did not get infected with COVID-19 (Helmich & Bloem, 2020). For this reason, in this review, pharmacotherapy of PD patients that links with COVID-19 will be discussed.

1.2 Aim of the study

This review aims to gather all possible information on the possible links in the mechanism of PD and COVID-19, consequences of PD patients infected with COVID-19, treatment options for PD and COVID-19, treatment of PD patients infected with COVID-19, also proper care of PD patients in the course of the COVID-19 pandemic.

1.3 Objectives of the study

The objectives of this review are,

- To compile information about the existing and emerging consequences of COVID-19 on PD patient's signs and symptoms.
- Collect information about the health status of PD infected with COVID-19 as well as the risk of COVID-19 in patients with PD.
- Gather all possible information of PD and COVID-19 treatment.
- To identify relationships between the treatment of PD and COVID-19.

Chapter 2

Methodology

A three-staged procedure was used to gather the information for this review which include: 1) using resources such as PubMed and ScienceDirect, I was compiled a list of potentially relevant papers, 2) selection of articles that are unquestionably relevant, and 3) scrutiny of selected studies. A review of articles was done to compile these recent advances. The articles were chosen based on the most recent information about pharmacotherapy of PD, PD pharmacotherapy that links with COVID-19, risk factors, treatment, etc. and for this review study, the above mentioned keywords were utilized to gather information . Finally, through Mendeley library the references were searched and inserted into the review paper. Also, a bibliography of all the references that have already been cited was created.

Chapter 3

Relationship between COVID-19 and Parkinson's disease (PD)

The first report on the relationship between COVID-19 as well as PD comes from the research on antibodies against four antigens of COVID-19 like human coronaviruses 229E along with OC43 in Cerebrospinal Fluid (CSF) of normal controls compared to patients with neurological illnesses, especially PD. Compared to many neurological illnesses, PD patients have higher CSF coronavirus antibodies (Butterworth, 2020). Functional connections between PD and COVID-19 occur in a variety of ways. CSF of patients with PD reports higher antibody responses to a range of coronaviruses (Fazzini et al., 1992), and in other viral encephalitides, the abnormalities of the basal ganglia have also been seen (Fishman et al., 1985).

3.1 Comparison between signs and symptoms of PD and COVID-19

Coronavirus causes a wide variety of symptoms such as fever, cough, shortness of breath, sputum, myalgia, joint pain (Fearon & Fasano, 2021). In addition, headache, diarrhea, and sore throat and they are the prevalent symptoms of this disease that occur 2-14 days after exposure (Wan et al., 2020; B. E. Young et al., 2020). On the other hand, PD signs and symptoms can be different for the individual and it develops gradually. PD usually starts with a slight tremor in one hand along with a sense of stiffness in the body. Over time, other symptoms will appear, and some people may develop dementia (Fearon & Fasano, 2021).

COVID-19 infection is closely related with the development of anosmia or hyposmia, particularly in women and patients with fever (da Silva et al., 2021; Lechien et al., 2020). On the other hand, anosmia or hyposmia is a typical non-motor symptom of PD and occurs in ~90% of early-stage cases of PD (Ponsen et al., 2004). Myalgia which is a painful condition that affects the back muscles is frequent with COVID-19 or other viral infections and in certain cases, COVID-19 patients with PD (Sulzer et al., 2020). In addition, fatigue is a typical

symptom of COVID-19 disease and the most prevalent and debilitating symptom of PD patients, affecting their quality of life significantly. Although pathophysiology of fatigue is poorly understood in PD (Kostić et al., 2016; Townsend et al., 2020).

Since SARS-CoV-2 infection symptoms such as pain in the limbs, fatigue, and anosmia are also part of the non-motor symptoms of PD, early and accurate diagnosis of SARS-CoV-2 in PD patients is difficult (Sulzer et al., 2020; Tarakad & Jankovic, 2017). Over 96% of PD patients suffer from anosmia and up to 40% of patients with loss of taste (Tarakad & Jankovic, 2017).

Table 1: Comparison between the signs and symptoms of COVID-19 and PD

COVID-19	**Parkinson Disease(PD)**
The most common symptoms (Alimohamadi et al., 2020), Fever Dry cough Fatigue **Symptoms that are less common and may affect some patients include** (*WHO,* 2020), Loss of taste or smell, Nasal congestion, Conjunctivitis, Sore throat, Headache, Muscle/joint pain, Nausea/vomiting, Diarrhea, Chills/dizziness. **Symptoms of severe COVID-19 disease include** (*WHO*, 2020) Shortness of breath, Loss of appetite, Confusion, Persistent pain/ pressure in the chest, Temperature above 38 °C	**Motor and Related Symptoms of PD** (Standaert et al., 2018), Tremor Rigidity Bradykinesia Postural Instability Walking/Gait Difficulties Vocal Symptoms **Non-Motor Symptoms of PD** (Standaert et al., 2018), Disturbances in the Sense of Smell Disturbance of the normal sleep pattern Depression with Anxiety Fatigue Cognitive Decline Loss of weight GI problems Light headedness Urinary Issues Sweating Melanoma

3.2 COVID-19 is related with an elevated risk of developing PD

According to a minimum of 3 revealed single-case within 2–5 weeks of receiving COVID-19 patient acquired clinical parkinsonism, either alone or with some neurological abnormalities (Brundin et al., 2020; S. Cohen et al., 2021). They (age 35, 45, and 58) required hospitalization because they suffered from a severe respiratory infection. Two of them reported a decrease in their parkinsonian symptoms after taking traditional dopaminergic medication (M. E. Cohen et al., 2020; Faber et al., 2020). The third patient recovered spontaneously (Méndez-Guerrero et al., 2020). In all of them, a decrease in the nigrostriatal dopamine system function was observed by brain imaging that is similar to PD. Among them, one was without PD risk variants found by genetic testing, and no one had a record of prodromal PD signs or record of PD in their family history (M. E. Cohen et al., 2020).

Perhaps, these patients were prone to develop PD and they were about to lose the number of nigral dopaminergic neurons necessary for motor symptoms to appear. Also, COVID-19 accelerated an ongoing neurodegenerative process. In the case of viral infection, the fast onset of serious motor symptoms still indicates a causal relationship. In addition, before COVID-19 disease no one among the patients reported signs of prodromal PD (Brundin et al., 2020).

One possible reason for the increased risk of dying from coronavirus in PD patients' might be that it can cause pneumonia, and pneumonia is the reason for death in PD patients. Part of the reason is that PD patients' may have difficulty in swallowing or suffocation, which may lead to aspiration (Zhang et al., 2020). Therefore, elderly patients are more prone to death because age is a risk factor of COVID-19 as it can lead to acute respiratory distress syndrome (ARDS) (Hainque & Grabli, 2020). Additionally, quarantine, pharmacodynamics effects and sudden changes in daily life, the effects of stress and anxiety, and inconvenience are the indirect effects

of COVID-19 that affect PD patients life and also create adverse effects on motor and non-motor symptoms (Helmich & Bloem, 2020).

Chapter 4

Potential mechanisms of PD development in COVID-19 patients

Many possible procedures have been suggested through which SARS-CoV-2 infection can affect PD or give rise to PD. These mechanisms can work individually or together. These include:

In the first place, in extreme COVID-19 cases, vascular harm was recorded to happen in numerous organs along with the cerebrum, in serious COVID-19 related to a hypercoagulable state. This may straightforwardly harm the nigrostriatal network, similar to what is viewed in vascular Parkinsonism (Faber et al., 2020).

Secondly, it is possible that severe COVID-19 causes marked systemic inflammation as it can activate neuroinflammation along with death of nigral dopamine neurons by taking in mind the link between inflammatory disorders as well as higher PD risk. It is believed that the midbrain is particularly sensitive due to dopaminergic neurons. In many studies, it was observed that level interleukin (IL)-6 has increased in COVID-19 (Thomas et al., 2020). Moreover, one among these studies observed perturbation in the kynurenine pathway. Interestingly, both of these mechanisms are related to PD (Heilman et al., 2020; Johnson et al., 2019). The metabolic pathway of tryptophan degradation is called the kynurenine pathway (KP). In patients with COVID-19 it is highly activated which leads modulation of the immune response as well as promotes cognitive dysfunction. Therefore, it is not clear whether KP activation in COVID-19 leads to an increase in the conversion of tryptophan to l-KYN. Contrarily, it is assume that the kynurenine pathway malfunctions in PD because of making excessive QUIN, dopamine-producing cell death and inflammation. Additionally, the levels of kynurenine metabolites could altered by L-DOPA treatment and it can affect the glutamatergic transmission that result L-DOPA-induced dyskinesia (LID). A study to look into the probable KYN metabolites role

in LID in which evaluation of KP metabolites in plasma and CSF from Parkinson's patients with LID showed a four-fold increase in the 3HK / KYNA ratio and a decrease in AA levels. 3-HAA causes oxidative stress in neurodegenerative disorders, leading to the reactive oxygen species production. TRP metabolism was affected by stochastic resonance therapy as it reduced the TRP, KYN and KYNA levels that might induce neuropsychiatric disorders such as PD (Collier et al., 2021; Venkatesan et al., 2020).

Thirdly, after the death of a few patients with coronavirus viral RNA was found in their brain so it can be assumed that COVID-19 could also be a neurotropic virus. In addition, in the olfactory system or enteric nerve PD process starts that has been shown in neuropathological studies on the immunostaining of aggregated α-synuclein, then spreads along the neural pathway to other areas of the brain (Poewe et al., 2017). Common characteristics of prodromal PD are hyposmia, constipation, additionally α-synuclein aggregates could contribute to the pathophysiology. The virus can directly enter the brain area associated with PD as the gastrointestinal tract is infected and hyposmia is common. The vagus nerve also innervates the airway. In addition, high levels of angiotensin-converting enzyme 2 (ACE2) receptors is expressed by dopamine neurons in the midbrain. It is needed for virus entrance, and may make cells sensitive to COVID-19 (Yang et al., 2020). The intriguing chance is that the neural intrusion of SARS-CoV-2 will prompt expanded neuronal articulation of α-synuclein during the viral disease of the sensory system, and α-synuclein will undergo increment and go about as an infection limitation factor. Like PD brain continuously increasing levels of α-synuclein in neurons is responsible for the formation of aggregates in SARS-CoV-2, which subsequently lead to neuronal death (Faber et al., 2020).

Thus, whereas acute brain disorder in association with coronavirus seems to be uncommon, and unfolding of COVID-19 in the community causes a big percentage of people to be prone to PD later in life, particularly as they will also be influenced by normal processes of aging.

Besides, it is mandatory to closely monitor the number of patients infected with the virus and keep track of the signs of PD. It will be strenuous to find the medication that reduces such rising risk (Faber et al., 2020).

Chapter 5

Effects of COVID-19 on PD patients

5.1 Consequences of PD patients with COVID-19 infection

Infection is a common reason for worsening parkinsonian symptoms. Therefore, infections like SARS-CoV-2 have harmful effect (it can be direct or indirect) on the motor symptoms of PD. A study found that in all eight COVID-19 patients, PD symptoms worsened sooner or later after infection (Artusi et al., 2020).

Twelve PD and COVID-19 patients were compared in a population-based study with 36 years old, sex, and COVID-related negative benchmark groups, and observed that levodopa-related motor symptoms declined and raised day by day OFF-time in the COVID-19 patients. A big part of COVID-positive cases experience diarrhea, and motor deterioration and apart from the deterioration of motor disability as well as everyday activities for living daily OFF time were mainly clarified by diarrhea (Cilia et al., 2020).

A survey on the telephone in Spain with 568 patients recorded that symptoms of PD deteriorated in 65.7% of people in the period of COVID-19 (Santos-García et al., 2020). Another study looked at consultations with PD people in Rome during the COVID-19 is related to plan activities (clinic visits, prescriptions, etc.) and identify acute clinical deterioration in 28% of people. Though nobody among them was troubled by the coronavirus pandemic, deterioration of motor symptoms was reported by 50% of them (an increase in dopaminergic therapy is a need in one-third), while 25% reported increased anxiety (Schirinzi et al., 2020). In a case-controlled survey in Tuscany, during the coronavirus pandemic, motor symptoms deterioration was recorded in 29.6% (N=733) of PD cohort (without COVID-19) with the same deterioration of 24.7% mood, 25% anxiety, and 22.2% sleep deprivation (Del Prete et al., 2020).

New motor symptoms were reported in 18% of patients and at least one existing motor symptom deteriorated in 55% of patients. New as well as worsening non-motor symptoms were reported in all areas: mood (new change 20%, deterioration 51%), cognitive function (new change 7.8%, deterioration 41%), sleep (new change 12%, deterioration 59 %)), and autonomic (7.8% new, 29% worsening) (Artusi et al., 2020).

Therefore, there is a piece of strong evidence that COVID-19 has direct and indirect effects on the motor and non-motor symptoms of PD. Compared with the virus itself, for PD patients the indirect effect of coronavirus is more harmful (Fearon & Fasano, 2021).

Elderly people might be susceptible to severe acute respiratory syndrome, especially those who have impaired cough reflex, advanced PD as well as respiratory muscle involvement. Before COVID-19, a study in Japan found that aged people with pneumonia and parkinsonism had a notably lower rate of mortality in the hospital than the people without it (Jo et al., 2018), this suggests that PD people might not be as susceptible as instinctively expected. However, patients' mortality rates in PD have been examined where only 8 studies found PD with COVID-19 and from these 8 studies, 5 are case series, involving 2 to 117 COVID-19 cases (Fearon & Fasano, 2021).

Four out of ten elderly PD patients with COVID-19 died (Average 78.3 years) from the UK and Italy. They also had advanced disease and two patients were treated with intrajejunal levodopa (Antonini et al., 2020). However, out of 6 patients, 2 patients recovered by being treated with advanced therapies (Fearon & Fasano, 2021).

During the COVID-19 pandemic, while comparing hospitalization of PD patients with the three-year follow-up period, the data found that there were 13 deaths in 22.4% of hospitalized patients, in comparison with 6.5% of previously hospitalized patients (Kobylecki et al., 2020). In the hospital mortality rate was 5.2% where there were only three deaths due to COVID-19.

This highlights the potentially serious adverse effects of delays in finding other medical conditions (such as heart disease) (Fearon & Fasano, 2021).

This period of COVID-19 for PD may be represented by the total excess of morbidity and mortality rather than the mortality rate in COVID-19. A multi-center investigation of one hundred seventeen local area residents COVID-19 positive PD patients in Italy, Iran, Spain, and the UK analyzed predictors of results (Fearon & Fasano, 2021). The overall rate of mortality was 19.7%, predictors of the poor outcome included coexistent dementia rate 26.1%vs. 8.5%, $p = 0.049$, PD time span was 11.7 ± 8.8 vs. 6 ± 5.4 years where $p = 0.029$, also expand mortality with hypertension that was 63.6%vs. 37.6%, $p = 0.054$. Therefore, although all-cause mortality is lower than in previous studies, patients with advanced PD are again at higher risk. In an earlier study, they noticed patients with PD and familial controls did not have a crucial distinction in death rates which was 5.7%vs. 7.6%, $p = 0.20$ (Fasano, Cereda, et al., 2020). Additionally, 14% (N-7) and 75% (N=8) rate of mortality was reported by two other Italian studies (Del Prete et al., 2020). In these studies, fewer numbers of infected people were included which focus on the struggles in making meaningful estimates of the results. Comparing the results of 29 severe COVID-19 positive PD people (admitted to the hospital or died) with 182 moderately COVID-19 / without COVID-19 patients, the results showed that there was a positive correlation between adverse effects and hospitalization (28% vs. 5 %, $p<0.0001$)), dementia (38% vs. 15%, $p=0.0026$), coexisting tumors (10% vs. 2%, $p = 0.0353$), as well as a negative connection with dopamine agonists use (17%vs. 74%, $p = 0.0155$), whereas there is no correlation with dementia and dopamine agonist use has been observed (Sainz-Amo et al., 2020). This study found 21% overall mortality.

The PD patients' mortality data with COVID-19 infection is still inconclusive, and the numbers are between 5.2% and 100% (Table-2). In the hospital mortality rate is higher in patients with the neurological disorder in comparison with non-neurological in COVID-19, ranging from

29.7% to 44.8% (Frontera et al., 2021; García-Azorín et al., 2020). In such situation, questionnaires along with telephone-based surveys are in danger of bias because they may overlook the most severe patients who have been sick for a long time. At the same time, hospitalized patients with minor cases might overestimate the overall mortality in such a specific cohort (Fearon & Fasano, 2021).

Table 2: Ongoing research on mortality data related to COVID-19 in PD

Study Design	**Total PD sample**	**PD**	**Controls**	**Risk factors**	**Reference**
Phone survey	1486 (105 COVID+)	5.7%	7.6%	NA	(Fasano, Cereda, et al., 2020)
Phone survey	1407 (8 COVID+)	75%	NA	NA	(Artusi et al., 2020)
Phone survey	740 (7 COVID+)	14%	NA	NA	(Del Prete et al., 2020)
Single-center case series	211 (33 COVID+)	21%	NA	Cancer, hospital admission (no DA use, dementia)	(Sainz-Amo et al., 2020)
Multicenter case series	117 (117 COVID+)	19.7%	NA	Dementia, hypertension, disease duration	(Fasano, Cereda, et al., 2020)
Inpatients	58 (3 COVID+)	5.2%	NA	NA	(Kobylecki et al., 2020)
Case series	10 (10 COVID+)	40%	NA	Age, disease duration, use of advanced therapies	(Antonini et al., 2020)
Case series	2 (2 COVID+)	100%	NA	STN DBS	(Hainque & Grabli, 2020)

Chapter 6

Treatment options for Parkinson's Disease and COVID-19 with possible interconnections

6.1 Currently available treatments for PD patients

Presently, no disease-modifying treatment is available for PD, so the treatment is mainly composed of dopaminergic drugs and most of time used drugs for these preparations are levodopa, the dopamine precursor and to reduce certain side effects like nausea these drugs are given in conjunction with a dopa-decarboxylase inhibitor (Stoker et al., 2018). Ropinirole and rotigotine, both dopamine agonists, are also used. Rasagiline and selegiline are examples of MAO-B (Monoamine oxidase B) inhibitors, and entacapone is the example of COMT (catechol-O-methyltransferase) inhibitors that could be used to decrease endogenous dopamine metabolism. In the striatum, these medicines restored dopaminergic activity that indicates motor characteristics development in PD patients. In some situations, these medicines are disabling for numerous people because of their incapability to cure several non-motor characteristics. Undeniably, motor symptoms like postural hypotension as well as neuropsychiatric issues could worsen due to the therapies in certain situations (Kujawa et al., 2000; B. K. Young et al., 1997).

Some motor characteristics of PD can be improved by these medicines. Besides, long-term use of levodopa (early stage) cause significant adverse effects. It is believed that the continuous flow of non-physiological dopamine into the striatum is responsible for the abnormal involuntary jerky movements also called dyskinesias and uncertain absorption of the drug is responsible for motor function fluctuations as well as into the brain irregular transit of levodopa, resulting in the so-called on-off phenomena (Nutt et al., 1984). Neuropsychiatric adverse effects like hallucinations and problems in impulse control could develop when these

drugs are delivered to the brain except the striatum as they cause off-target effects (Stoker et al., 2018; Voon et al., 2009).

To control the movement disorder of PD, deep brain stimulation (DBS) is another valid way. Unfortunately, for several non-motor indications, it does not work well (Kalia et al., 2013), and only for a few PD cases, this medication is appropriate. However, speech difficulty and psychological disruption, as well as the general hazards involved with a neurosurgical surgery are additional potentially significant adverse effects of it though the method is risk free (Benabid, 2003).

One strategy of conveying dopamine more physiologically could be the levodopa-intestinal gel use, and it leads to a better prediction of dopamine release than oral formulation. Motor adverse effects of dopaminergic medication could decrease by this method. Unfortunately, for general usage, it is prohibitively costly and fraught with difficulties due to the surgery required for installation (Olanow et al., 2014). Furthermore, it is unacceptable for many people to connect with a device that should endue regularly like DBS and apomorphine pumps (Stoker et al., 2018).

So, while there are successful therapy choices for the motor characteristics of PD, they come with major drawbacks, and none can reduce disease progression or ameliorate the debilitating non-motor symptoms (Stoker et al., 2018).

Table 3: Clinically available anti-Parkinson's drugs, their adverse reactions (ADR) and mechanism of actions (MOA)

Drugs	MOA	ADR	References
Levodopa	DOPA decarboxylase in the dopaminergic neuron of the CNS metabolizes this prodrug to dopamine.	Anorexia and nausea, hypotension, tachycardia and ventricular extra systoles, anxiety, depression, mood change and psychosis	(Handa et al., 2019; Jost et al., 2020; Nakaki, 2017)
Entacapone and Tolcapone	Inhibit levodopa metabolism produced by COMT.	Postural hypotension, diarrhea, nausea, anorexia along with dyskinesia, hallucination and sleep disorder in varying doses	(Castro Caldas et al., 2018; Ha et al., 2017; van der Velden et al., 2018)
Bromocriptine, Ropinirone, Pramipaxole, Rotigotine and Apomorphine	Dopamine agonists	Sedation, hallucination, confusion, nausea and hypotension, pulmonary and retroperitoneal fibrosis	(Borovac, 2016; Siddiqui et al., 2018; You et al., 2018)
Selegiline and Rasagiline	Selectively block MAO-B, resulting in an increase in dopamine levels in the brain.	Hypertension; insomnia in many patients	(Anwar et al., 2020; Bundgaard et al., 2016; Finberg, 2019; Sridhar et al., 2018)
Amantadine	Dopamine release is increased, cholinergic receptors are blocked, and NMDA receptors are inhibited.	Hallucination, confusion, agitation, and restlessness.	(Fryml et al., 2017; Nikolaus et al., 2019; Oertel et al., 2017)
Benztropine, Trihexyphenidyl, Procyclidine and Biperiden	Antimuscarinic medications inhibit acetylcholine receptors and restore the acetylcholine/dopamine ratio equilibrium.	Constipation, dryness of mouth and visual disturbance in PD patients.	(Kim et al., 2017; Nishtala et al., 2016)

6.2 Repurposed drugs for COVID-19

Currently there are no medicines that have therapeutic or preventive effects in patients infected with or suspected of having COVID-19. Hundreds clinical trials should be done by using existing repurposed drugs. In the current context, drug repurposing might be viewed as a potential therapy option for COVID-19 (Anwar et al., 2020).

Remdesivir is now licensed for the treatment of COVID-19. It is a prodrug that is activated to C-adenosine triphosphate and have selective action against host polymerase against RNA viruses such as Coronaviridae and Flaviviridae, including the Ebola virus (Barkoff & Mousa, 2021). At present, no curable drugs available for COVID-19 disease as a result researchers are testing a variety of possible treatments (Anwar et al., 2020). Some of these are mentioned below,

6.2.1 Favipiravir (FPV)

According to information collected by Dong and colleagues from a Chinese news station, favirpiravir was approved for use against SARS-CoV-2 infected patients in China on February 15, 2020, because it significantly reduced the disease of SARS-CoV-2 infected patients (Dong et al., 2020). It operates by blocking the enzyme RNA polymerase (Zhao et al., 2015).

6.2.2 Monoclonal Antibodies

COVID-19 possesses a spike protein on its surface that aids viral attachment and entry into human cells. A few monoclonal antibodies have been designed that attach with the viral spike protein and prevent it from infecting cells of human. An intravenous (IV) infusion of a monoclonal antibody can be given to a coronavirus infected patient. Bamlanivimab plus etesevimab as well as casirivimab plus imdevimab are two combination items approved by the FDA for the treatment of mild to moderate COVID-19 in non-hospitalized patients with

laboratory confirmed SARS-CoV-2 infection who are at high risk of progressing to severe disease and/or hospitalization (Lloyd et al., 2021).

6.2.3 Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Emergency use of CQ and HCQ has been stopped for the coronavirus positive patients by the United States Food and Drug Administration. CQ and HCQ both are weak bases that raise the acidic intracellular organelles pH for example lysosomes/endosomes, which require a low pH for development as well as function. Furthermore, CQ was discovered to generate alterations in the glycosylation of the ACE2 spike protein and receptor, which eventually prevents the entry step and the post-entry phase of COVID-19 and HCQ demonstrated the capacity to exert the same mechanism (Saghir et al., 2021).

6.2.4 Convalescent plasma transfusion

It is useful for severely ill COVID-19 patients (Shen et al., 2020) and already been utilized in the treatment of SARS infection. In one uncontrolled research of five severely sick COVID-19 patients, the delivery of plasma containing neutralized antibodies demonstrated encouraging effects in terms of these patients' clinical state (Chen et al., 2020). A meta-analysis of plasma treatment for SARS as well as influenza found that it was related with a lower death rate (95 percent CI), minimal side effects, and a low risk. However, the efficacy of plasma treatment in PD patients with COVID-19 is yet unknown and is under clinical trial (Parker et al., 2020).

6.3 Drugs for PD patients infected with COVID-19

6.3.1 Favipiravir (FPV)

It is difficult to determine the appropriate dose of favipiravir for those above the age of 60, particularly PD sufferers because most of the PD patients might have one or more chronic disease such as hypertension, diabetes along with other complications (Anwar et al., 2020). Also, COVID-19 is frequently linked with acute respiratory distress. So, it is very

crucial to understand the drug interaction for such patients. Favipiravir interacts with acetaminophen because of the inhibition of sulphate transferase in the liver, which makes it very important to understand the drug interaction for the PD patients before recommending this drug. Aldehyde oxidase (AO) metabolizes FPV in the cytosol. PD patients on any of AO inhibitors like cimetidine, calcium channel blocker, antiarrhythmic drug propafenone or any other tricyclic antidepressant need to adjust the dose before going for FPV (Zhao et al., 2015).

6.3.2 Azithromycin (AZM)

In the treatment of lung infection, AZM is also found to have anti-inflammatory action via suppressing IL-6. This impact has the potential to alleviate the inflammatory process produced by COVID-19 (Gérard et al., 2020). Thus, it functions as a medication with the ability to eliminate senescent cells up to 97 percent of the time. It works as an anti-fibrotic agent in cystic fibrosis patients by targeting myofibroblast cells. Fibrosis is an age-related condition characterized by an enhancement in the number of myofibroblast cells (Song et al., 2020). PD is also an age-related condition, and an increase in myofibroblast cells cannot be ruled out in such individuals. It has been demonstrated that AZM, a regularly used antibiotic that suppresses viral replication and IL-6 production, can be utilized as an option in the treatment of COVID-19 illness in PD (Anwar et al., 2020).

6.3.3 Amantadine

Amantadine was the first FDA-approved medicine in the United States, and it is the only medicine that indicates its dual function in PD and COVID-19 treatment (Anwar et al., 2020; Aranda-Abreu et al., 2021). It affects various neurotransmitters implicated in PD, including an increase in dopamine release (Nikolaus et al., 2019), blocks cholinergic receptors (Fryml et al., 2017), and inhibits N-methyl D-aspartate (NMDA) receptors (Oertel et al., 2017). Thus, it was

employed to counteract the effects of COVID-19 through two separate processes (Butterworth, 2020), namely:

Down-regulation of host cell proteases not restricted to cathepsin L because inadequate fusion of viral and host cell membrane that leads to impaired viral genome release into the host cell's cytoplasm. Reduced viral entry can reduce viral load in COVID-19 patients, leading to improved clinical outcomes. To determine the amantadine therapeutic effectiveness for COVID-19 positive patients appropriately planned, proper clinical studies are required (Butterworth, 2020).

It is a potent noncompetitive NMDA receptor antagonist. Experiments on coronaviruses showed these type of antagonist can restrict viral replication as well as develop neurological symptoms. In mammalian lungs and airways these receptors were found. Also, in various kinds of acute lung damage and pathogenesis of the acute respiratory distress syndrome these potent noncompetitive NMDA receptor antagonist is worked by the activation of NMDA receptors (Li et al., 2020).

However, this medication has been linked to side effects such as hallucination, disorientation, anxiety, and restlessness (Grieb et al., 2021).

6.3.3.1 Link among Amantadine, COVID-19 and PD

Amantadine is advantageous due to its promotion of dopaminergic synaptic activation. Several processes, including increased dopamine synthesis, turnover, and release, have been hypothesized. Positron Emission Tomography (PET) studies in Parkinson's disease patients give data consistent with the idea that amantadine increases dopamine production as a result of antagonism of the NMDA subtype of glutamate receptors in the brain (Deep et al., 1999; Kong et al., 2017).

Even though it has not been resolved whether amantadine's NMDA receptor antagonist property is related with protective effect against COVID-19 or its neurological intricacies, there is proof to recommend that NMDA receptor antagonist might be useful as a medication of other coronaviruses. For instance, the human coronavirus strain HCoV-OC43 can affect neural cells where it initiates neuroinflammatory along with neurodegenerative systems and non-competitive NMDA receptor antagonist memantin (same structure of amantadine) can restrict viral replication and enhance neurological indications of HCoV-OC43-infected mice. Besides, NMDA receptors in the lungs along with airway may support the signaling mechanisms involved in the pathogenesis of acute lung injury as well as the acute respiratory distress syndrome (ARDS) which is normal for coronavirus infections (Butterworth, 2020; Desforges et al., 2019).

Chapter 7

Impact on PD patient care due to COVID-19 Pandemic

COVID-19 has been a big issue for people with PD because it is related to neurological symptoms though it is a respiratory disorder. Because of the COVID-19, the medical care of PD patients has been affected throughout the globe though it is not frequent like other diseases (Elbeddini et al., 2020).

7.1 Effects of social distancing and lockdown on PD patients' health

Social isolation and its impact on PD are a matter of concern and are called the "hidden sorrow" of the pandemic. Also, it is responsible for increased anxiety, worsening of depression that existed previously, the negative consequence of stress on PD, and a lack of physical activity like exercise. One in every three patients in the hospital developed a posttraumatic stress disorder, with 15% acquiring despair and anxiety after a year, and more than 15% experienced exhaustion during the earlier SARS and MERS epidemics (Rogers et al., 2020). Due to the coronavirus-related lockup, anxiety and subsequent stress in PD patients have been observed in many countries by telephone consultations (Sulzer et al., 2020).

The coronavirus pandemic has brought about huge changes to the normal schedules of Parkinson's disease patients, with social separation and lockdowns set up around the world. Numerous PD patients suffer from a detrimental influence on mental health. In comparison to matched controls PD patients' experienced greater stress, sadness, anxiety, and quality of life throughout the pandemic which is reported by a movement disorder clinic in Cairo (Shalash et al., 2020).

7.1.1 Stress

The danger of chronic stress is intrinsically raised because of the pathophysiology of PD which decrease the level of dopamine that affects the mechanism of stress management (Helmich & Bloem, 2020). Stress is an alarming issue for PD people as it is responsible for both acute and long-term repercussions for PD sufferers. Motor symptoms like tremor, gait and dyskinesia can be worsen by physiological stress (Hemmerle et al., 2012). Dopaminergic drugs effect decreased by stress, for example levodopa effects on Parkinson's tremor (Zach et al., 2017). A latent a hypokinetic-rigid syndrome might be revealed by increased stress, Probably leading to new Parkinson's disease diagnosis during COVID-19 (Bhidayasiri et al., 2020).

7.1.2 Anxiety

In PD patients' anxiety is the most prevalent neuropsychiatric problems. During the pandemic, 25.5 percent of cases recorded severe anxiety and 4.8 percent of controls in PD people along with the age-coordinated general public in Iran (Salari et al., 2020). There was a strong association between the anxiety intensity in people with PD along with their fear of coronavirus infection, which was much greater than in controls (Schirinzi et al., 2020).

7.1.3 Reduced Mobility

During the pandemic, preventative measures decreased mobility and physical activity that is responsible for lazy and inactive lifestyles. It is significant because physical activity can reduce clinical PD symptom development and related stress (Helmich & Bloem, 2020). Hence, promoting home-based workouts like virtual fitness exercise can play significant role in keeping up with the general wellbeing of PD patients during COVID-19 period (Elbeddini et al., 2020).

Anxiety, stress, loneliness, and physical inactivity are more harmful when combined in PD patients (Helmich & Bloem, 2020). Chronic stress has promoted dopaminergic cell death in

PD experimental mice perhaps, exacerbating the neuropathological alterations that cause the disease (van der Kolk et al., 2019).

7.2 Breakdown of the medical care system

The coronavirus pandemic has an indirect impact on PD sufferers as it produces disruption in medical-care systems. For the care of PD patients neurologists play a vital role (Papa et al., 2020). But, there is a shortage of neurologists, who may have to care for COVID-19 patients, particularly in areas where medical personnel are few. This has reduced time for PD patient's care. Non-urgent surgical operations have been postponed in several medical communities to avoid patients from becoming infected. DBS, the initiation of LCIG, and apomorphine pumps that are elective surgical operations have been postponed in PD patients (Fasano, Antonini, et al., 2020). Perhaps, this leads to increased PD symptoms as these delays prevent PD patients from getting critical drugs that help control their illness. However, there was no negative effects of COVID-19 on the worldwide delivery of medicine for PD patients (Papa et al., 2020).

7.3 Health care system shifted to virtual care for PD Patients

One other impact of the coronavirus pandemic is the quick adoption of telemedicine in various medical-care systems, and to offer virtual care communication technology is employed. Numerous PD patients and neurologists have changed to telemedicine arrangements, especially coordinated videoconferencing. Telemedicine and telerehabilitation have been widely researched and verified for usage in assessing PD patients (Chirra et al., 2019). However, because muscular stiffness and retropulsion pull tests cannot be correctly assessed through videoconferencing the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is not suggested for virtual examinations (Fasano, Antonini, et al., 2020; Goetz

et al., 2020). Rather, a modified version of the MDS-UPDRS that does not include stiffness and retropulsion pull tests is used (Abdolahi et al., 2013).

Telemedicine benefits are access to experts, comfortable, saves time, and less expensive (Adams et al., 2020). Nonetheless, telemedicine has certain limitations. In telemedicine the main problems are lack of active care, inadequate intimacy and technical challenges and 781 people with PD reported this as they joined in an online survey (Spear et al., 2019). Providing virtual care is difficult for less developed nations because ensuring good internet connection and video with higher quality is not easy for them. Nowadays emails are widely available so it is possible to avoid this issue by communicating with neurologists through email, for example to capture symptoms of PD asynchronous videos could be utilized (Adams et al., 2020).

Remote treatment is practical, effective and helpful for PD people (Adams et al., 2020). However, it is crucial to consider the vital limitations to these studies. Candidates had usually mild disease severity with UPDRS part III scores ranging from 24.2–44.1 (128 maximum), also lived in advanced nations such as the United States, Canada, Italy, and Japan, suggesting that the PD population may be underestimated (Adams et al., 2020). More serious patients with chronic tremor, stiffness, and speech problems who were not represented in the research may have a variety of issues navigating telemedicine. Future study with complicated PD cases and those living in under developed nations is needed to acquire a good comprehensive knowledge about telemedicine role in PD patient treatment (Elbeddini et al., 2020).

Telemedicine still not established for therapies that requires devices like DBS or infusion pump devices as a result virtual management of devices in this therapies is a big challenge (Papa et al., 2020). Patients must be taught to change device settings, check battery life, and solve device faults. With these additional obstacles, improvement of remote access to device programming interest is growing that might reduce the technical load on PD patients (Elbeddini et al., 2020).

7.4 Slow progress in novel PD treatment because of COVID-19

One more unintended outcome of the SARS-CoV-2 virus is the influence on PD analysis and treatment trials. Because of COVID-19, several biopharmaceutical firms have postponed timetables for pipeline Parkinson's treatments. Also, it may impose an extra load on patients whose Parkinsonism could not be managed by the existing drugs in the drugstore. So, five pipeline drugs are discussed here.

i. Firstly, The FDA authorized Neurocrine Bioscience Inc's innovative medicine ONGENTYS (opicapone) as an add-on therapy to levodopa/carvidopa in Parkinson's disease people suffering "off" periods, although its sale in the US will be delayed owing to COVID-19 (Elbeddini et al., 2020).

ii. Secondly, the starting of a Phase IIb/III clinical study of dipraglurant, a new orally accessible metabotropic glutamate receptor 5 (mGluR5) inhibitor has been delayed by Addex Therapeutics, for (PD) people with levodopa-induced dyskinesias (Elbeddini et al., 2020).

iii. Thirdly, for Denali Therapeutics' backup pipeline drug DNL151 the entrance for Phase 1 as well as Phase 1b trials was halted. This tiny chemical inhibits LRRK2 that is a catalyst implicated in lysosomal dysfunction and neurodegeneration (Elbeddini et al., 2020).

iv. Fourthly, patient enrolment in the Phase II RESTORE-1 Trial Neurocine's NBIb-1817 experimental gene therapy medication has temporarily halted. To transfer the aromatic l-amino acid decarboxylase (AADC) gene into putamen neurons (directly) is the goal of this innovative therapy, where the AADC enzyme would generate to convert levodopa to dopamine (Elbeddini et al., 2020).

v. Fifthly, in the proceeding Phase of the 1b/2a trial of RTB101 in PD people resTORbio has revealed slowdown in enrollment of its 5^{th} cohort. RTB101 is a tiny chemical molecule that deters the rapamycin complex 1 (TORC1), which helps in decreasing neurologic function (Elbeddini et al., 2020).

Unfortunately, these delays may have a severe impact on patients who are desperate for novel Parkinson's disease medications to control their illness.

Chapter 8

8.1 Conclusion

The coronavirus pandemic has impacted all aspects of the healthcare system due to its uncertainty. People with neurological disorders especially PD patients suffer a lot because of COVID-19. Besides, early detection of COVID-19 in PD patients is difficult because of the similarities in their sign and symptoms. At the same time, COVID-19 increase the rate of mortality in patients with PD as it increase the chance of pneumonia and worsen the motor symptoms. Elderly patients are more prone to death because age is a risk factor of COVID-19 as it can lead to acute respiratory distress syndrome (ARDS). For PD, currently there is no disease modifying treatment and most of the drugs are used to reduce the symptoms to give temporary relief. For COVID-19 there is also no medicines that have curable therapeutic or preventive effects on patients. Luckily, amantadine is the only medicine that indicates its dual function in PD and COVID-19. Because of the COVID-19 pandemic, the medical care of PD patients has been affected throughout the globe as people with PD are more sensitive to the direct and indirect effects of COVID-19. Slow progress in novel PD treatment is one effect of COVID-19. Because of the speed with which COVID-19 has spread over the world, establishing big well-designed studies to investigate these problems in a scientific manner has been difficult. Recently available treatment options, clinical signs and symptoms, and several mechanisms are still necessary. However, social isolation and its impact on PD are a matter of concern as it is responsible for increased anxiety, worsening of depression, and stress on PD patients. Finally, it can be concluded that the purpose of this review is to identify the treatment options of PD patients with or without COVID-19, impact and consequences of COVID-19 pandemic on PD patients. The significant prognostic adverse effects of COVID-19 on PD and the present-day treatment options, clinical presentation and various mechanisms still remain the need of the hour.

8.2 Future Directions

This review has been written with a view to facilitate the work of future researchers who want to conduct research on the possible links in the mechanism of PD and COVID-19, treatment of PD patients with COVID-19, and proper care of PD patients in the COVID-19 pandemic. Besides, the information about treatment of these diseases will help them to write more informative research papers as well as possible interaction among drugs will be revealed to the people of the world. Moreover, it will serve as a future documentation for other researchers as well.

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